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Unipolar mania: Identification and characterisation of cases in France and the United Kingdom

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Abstract

Background: Unipolar mania is a putative subtype of bipolar disorder (BD) in which individuals experience recurrent manic but not major depressive episodes. Few studies of unipolar mania have been conducted in developed countries and none in the UK. This study aimed to identify and characterise people with unipolar mania in the UK and France. **Methods:** People with unipolar mania were ascertained using a South London UK electronic case register and a French BD case series. Each unipolar mania group was compared to a matched group of people with BD who have experienced depressive episodes. **Results:** 17 people with unipolar mania were identified in South London and 13 in France. The frequency of unipolar mania as a percentage of the BD clinical population was 1.2% for the South London cohort and 3.3% for the French cohort. In both cohorts, people with unipolar mania experienced more manic episodes than people with BD, and in the French cohort were more likely to experience a psychotic illness onset and more psychiatric admissions. Treatment characteristics of people with unipolar mania were similar to people with BD except that the unipolar mania group was less likely to be treated with antidepressants. **Limitations:** The relatively small number of people with unipolar mania identified by this study limits its power to detect differences in clinical variables. **Conclusions:** People with unipolar mania can be identified in France and the UK, and they may experience a higher frequency of manic episodes but have similar treatment characteristics to people with BD.

Keywords: Unipolar mania, Bipolar disorder, characteristics, identification

Introduction

Mania is the defining phase of bipolar I disorder. Recent studies indicate that mania may be inherited independently to depression and as such mania may be the behavioural phenotype of a distinct underlying neurobiological pathway (Merikangas et al., 2014). An important way to better understand bipolar disorder, interrogating this pathway, would be to dissect the broad bipolar phenotype by investigating people with unipolar mania who experience recurrent episodes of mania but not major depressive episodes. Investigating the clinical characteristics of people with unipolar mania is also important as they may have different care needs and risk profiles compared to people with bipolar disorder who also experience depressive episodes. The concept of unipolar mania dates back to Kraepelin (Mehta, 2014) although in modern diagnostic criteria unipolar mania is conceptualised as a subtype of bipolar I disorder (DSM-5) or as bipolar type I disorder, unspecified (ICD-11). Perhaps because of the lack of a distinct diagnostic category, there has been a little research into unipolar mania particularly in urban populations in developed countries. Most studies have been conducted in developing countries where rates of unipolar mania have been reported to be much higher than those in developed countries (Yazici, 2014).

In the past 25 years only six studies have investigated unipolar mania in developed countries (Angst et al., 2004; Baek et al., 2014; Douki et al., 2012; Perugi et al., 2007; Shulman and Tohen, 1994; Solomon et al., 2003), and none have investigated unipolar mania in a United Kingdom population. The studies that are available have used differing criteria due to a lack of a consensus unipolar mania definition. Although all studies based their definition on the absence of a depressive episode, with some additionally excluding people who have experienced mixed episode, criteria differ in the minimum number of manic episodes experienced (1 in older studies but 3-4 in more recent studies) and duration of required follow-up (minimum of 4-5 years follow-up or at least 10 years of total illness duration) (Yazici, 2014). The unipolar mania studies available from both developed and developing countries indicate that people with unipolar mania may have an earlier age of illness onset and experience more psychotic symptoms but experience less suicidality and co-morbid anxiety disorders. They may also have better outcomes with better social and professional adjustment (Yazici, 2014).

The aim of this study was to identify people with unipolar mania in the United Kingdom and France and to characterise their demographic, symptom and treatment profiles. Based on previous studies, we hypothesised that people with unipolar mania would be more likely to experience a history of psychosis and an earlier age of onset of bipolar disorder but would be less likely to experience self-harm or anxiety disorders than people with bipolar I disorder who have experienced depressive episodes.

Method

People with unipolar mania were identified and characterised in two populations: a retrospective case control series of people with bipolar disorder in the South London and Maudsley NHS Foundation Trust (SLaM) Biomedical Research Centre (BRC) Case Register, London, UK (Cohort 1) and a case series of French people of Caucasian ethnicity with bipolar disorder (Cohort 2). The definition of unipolar mania used for both cohorts was: a history of at least three manic episodes, no history of depressive or mixed episodes and a duration of illness lasting at least 10 years. This criterion is similar to that used by Perugi et al. in a previous unipolar mania study (Perugi et al., 2007) but also requires exclusion of people who have experienced at least one mixed episode as an additional criterion. We chose to use a minimum duration of illness of 10 years as an inclusion criterion, rather than a 4- or 5-year duration used in other studies, to increase the stability of diagnosis and minimise the likelihood that identified people with unipolar mania will subsequently experience a depressive episode.

Cohort 1

For the South London cohort, people with unipolar mania and matching bipolar disorder controls who have experienced depressive episodes were identified using the SLaM BRC Case Register between January 2016 and August 2018. The SLaM BRC case register is the largest regional register in Europe with records of over 300,000 individual cases representing the total secondary care use of mental health services for a population of 1.1 million in an urban population located in South London (Perera et al., 2016). The Case Register comprises anonymised mental health patient records derived from electronic clinical records used across SLaM and is accessed through the Clinical Record Interactive Search (CRIS). CRIS allows researchers to search against any combination of structured and unstructured fields from electronic clinical records (Stewart et al., 2009). A CRIS search automatically captures demographic details of identified individuals and supports the manual extraction of clinical variables. The resource has previously supported research studies investigating bipolar disorder (Patel et al., 2015a; Patel et al., 2015b). The CRIS data resource received ethical approval as an anonymised data-set for secondary analyses from Oxfordshire research ethics committee (Ref: 08/H0606/71+5) and the study proposal was reviewed and approved by the BRC CRIS Oversight committee.

People with unipolar mania were identified by performing a CRIS search using the following criteria: patients diagnosed with ICD-10 diagnosis of a manic episode (F30.0-9); or bipolar affective disorder, current episode manic or hypomanic (F31.0-2); or bipolar affective disorder currently in remission, other bipolar affective disorder, or bipolar affective disorder unspecified (F31.7-9); and who had never been diagnosed with schizophrenia (F20.0-9), schizoaffective disorders (F25.0-9), depressive disorders (F32.0-9, F33.0-9) or bipolar affective disorder current episode depression or mixed (F31.3-6); and who had at least 10 years of clinical follow-up to ensure the

10 years of duration of illness. In the identified sample, a keyword search of “Helpless, Hopeless, Worthless, Social Withdrawal, Apathy, Low mood, Sad, Tearful, Anhedonia, Depression, Depressive, Antidepressant” was conducted in the events and correspondence electronic patient record fields. Texts with a keyword hit were then read manually to ensure that any depressive episodes and/or symptoms were not missed by the CRIS search and that remaining patients with bipolar disorder who had experienced depressive episodes or symptoms were excluded.

People with bipolar disorder who have experienced at least one depressive episode and at least 10 years clinical follow-up were matched by age, gender and ethnicity to the unipolar mania group. A second CRIS search to identify this comparator group was used: patients with at least 10 years follow-up, receiving an ICD-10 diagnosis of a manic episode (F30.0-9) or bipolar affective disorder (F31.0-9), and never being diagnosed with schizophrenia (F20.0-9) or schizoaffective disorder (F25.0-9). The demographic details of this clinical South London bipolar disorder population were extracted from automatically generated CRIS data. Patients with bipolar disorder were then matched by age (± 5 years), gender and ethnicity group (white, mixed, Asian or Asian British, Black or Black British, other) to individual unipolar mania patients. The correspondence and event notes of the possible matches (starting from the nearest age and ethnicity match to their unipolar mania counterparts) were manually read to ensure the presence of at least one depressive episode and that sufficient clinical information was recorded.

The following variables were identified and extracted by reading the anonymised electronic clinical record correspondence and event notes for each unipolar mania and matched bipolar disorder patient: date of first and last recorded clinical contact, type of report available, current age, gender, ethnicity, year of symptom onset, recorded diagnosis, number and type of mood episodes, Care Programme Approach (CPA) status, number of voluntary and involuntary psychiatric admissions, history of psychotic symptoms, history of self-harm, history of substance use and associations with mood episodes, urine drug test results recorded during admissions, current and previous medication history.

Cohort 2

The French retrospective bipolar disorder lifetime descriptive case series was used to identify and characterise people with a DSM-IV diagnosis of bipolar I disorder who fulfil unipolar mania criteria. This cohort has been fully described by Drancourt and colleagues (Drancourt et al., 2013). Briefly, the cohort comprises Caucasian French individuals who met DSM-IV criteria for bipolar I or II disorder recruited from three general adult psychiatry follow-up clinics. This study was approved by the Comité de Protection des Personnes from La Pitié-Salpêtrière Hospital (reference: P111002-IDRCB2008-AO1465-50) in Paris, France. All participants provided written informed consent prior to inclusion. This study was primarily designed to identify genetic and environmental risk factors in bipolar disorder (ClinicalTrials.gov Identifier:

NCT02627404). Each participant was assessed by a trained psychiatrist using the Diagnostic Interview for Genetic Studies, a structured schedule that provides a retrospective lifetime description of bipolar disorder and other axis I disorders, and this was supplemented by detailed recording of treatment history. People with a diagnosis of bipolar II disorder, those with a diagnosis of bipolar I disorder with a lifetime history of two or less manic episodes and no depressive episodes, and those with less than 10 years duration of illness were excluded. The remaining patients were either patients with a lifetime history of at least three manic episodes but no depressive or mixed episodes (unipolar mania group) or those with a lifetime history of at least one depressive and manic episode (bipolar group). The following variables were extracted for individuals identified within the cohort: age, gender, age at onset, duration of illness from first mood episode, number of manic episodes, number of hypomanic episodes, number of major depressive episodes number of hospitalizations, number of suicide attempts, psychotic symptoms at onset of illness, any experience of psychotic symptoms, history of cannabis misuse, history of any substance misuse, history of any anxiety disorder.

Statistical analysis

Differences in continuous variables between groups were examined using t-tests and are reported as mean \pm standard deviation. Differences in categorical data were analysed using Chi squared or Fishers exact test when expected counts were less than five. Given the exploratory nature of this study, the statistical threshold used was $p < 0.05$ uncorrected for multiple comparisons. All statistical analyses were performed using SPSS (SPSS, Chicago, Illinois, USA).

Results

Cohort 1

The initial CRIS search identified 2920 people with a diagnosis of bipolar disorder, mania or hypomania and no previous documented episodes of depression. 2360 people were excluded as they had a follow-up duration of less than ten years leaving 560 potentially suitable people. Of these, 15 survived the exclusion process. 513 people were excluded because of a reference to a major depressive episode or depressive symptoms in the search of case records, 12 were excluded because of a primary diagnosis other than bipolar disorder (schizophrenia, schizoaffective disorder, learning disability, substance use disorder), and 20 because of insufficient clinical information. During the matching process, 2 additional people with unipolar mania were identified and the final sample consisted of 17 people with unipolar mania (see Figure 1).

INSERT FIGURE 1 HERE PLEASE

The CRIS search for bipolar I disorder patients who could be possible matches to the unipolar mania group identified 6637 people, 1458 of who had at least a 10-year

clinical follow-up (see Figure 2). The mean age of this bipolar clinical population was 54.3 ± 14.5 years, 569 men (39%) and 889 women (61%). The unipolar mania group did not differ in gender compared to people with bipolar I disorder with at least 10 years of clinical follow-up (unipolar mania 59% male, bipolar disorder 39% male, $p < 0.1$) but they did have a significantly different ethnicity profile with 59% of the unipolar mania group being African in ethnicity and 12% being British, compared to 6% and 52% for the overall South London bipolar population ($p < 0.001$).

INSERT FIGURE 2 HERE PLEASE

The unipolar mania and matched bipolar groups were well matched for age (mean age unipolar mania 49 ± 11 , mean age bipolar disorder 49 ± 10 , $p = 0.97$), gender (10 males in each group), and ethnicity (unipolar mania: 10 African-Caribbean, 1 Other Black, 3 Asian, 1 Mixed, 2 British; bipolar disorder: 8 African-Caribbean, 3 Other Black, 3 Asian, 1 Mixed, 2 British; $p = 0.96$). People with unipolar mania experienced significantly more manic episodes than the bipolar disorder group (unipolar mania 7.4 ± 4.5 , bipolar disorder 4.3 ± 2.0 , $p = 0.017$) and experienced significantly fewer recorded hypomanic episodes (unipolar mania 0, bipolar disorder 0.6 ± 1.2 , $p = 0.036$) (See Table 1 and Figure 3). Both groups experienced a similar number of total mood episodes (unipolar mania 7.4 ± 4.5 episodes, bipolar disorder 9.6 ± 4.4 episodes, $p = 0.15$). There were no differences between the two groups in age of onset, duration of illness, history of self-harm, history of suicide attempts, or the number or type of psychiatric hospital admissions. There were also no differences in substance use or anxiety disorders or medical illness co-morbidities. People with unipolar mania did not differ from people with bipolar disorder in their current or lifetime histories of treatment with antipsychotics (typical or atypical), mood stabilisers, long acting injectable antipsychotics, number of psychiatric medications currently taken or number of people not currently taking any psychiatric medications.

INSERT TABLE 1 AND FIGURE 3 HERE PLEASE

Cohort 2

392 patients with bipolar I disorder were identified from the French sample, and of these 13 fulfilled unipolar Mania criteria and 379 experienced at least one depressive episode. The demographic, clinical and treatment characteristics of these two groups are shown in Table 2.

INSERT TABLE 2 HERE PLEASE

There was no significant difference between the unipolar mania and bipolar groups in age or gender. People with unipolar mania experienced significantly more manic episodes (unipolar mania 6.5 ± 4.3 , bipolar disorder 2.6 ± 2.4 , $p = 0.0001$) but did not experience more hypomanic episodes (unipolar mania 5.6 ± 7.2 , bipolar disorder 1.5 ± 2.8 , $p = 0.29$) (See Figure 2). There were no differences between groups in the total number of major mood episodes experienced (unipolar mania 6.5 ± 4.3 episodes,

bipolar disorder 6.5 ± 4.1 episodes, $p=0.99$). People with unipolar mania were more likely to experience psychotic symptoms during their first mood episode (unipolar mania 62%, bipolar disorder 22%, $p=0.003$). There were no differences between the two groups in age of onset, duration of illness, history of psychosis, history or number of suicide attempts. People with unipolar mania experienced significantly more psychiatric hospital admissions (unipolar mania 8.0 ± 6.4 , bipolar disorder 4.1 ± 4.2 , $p=0.007$). There were no differences in anxiety or addictions co-morbidity between the two groups.

People with unipolar mania were significantly less likely to have lifetime history of antidepressant (unipolar mania 25%, bipolar disorder 90%, $p=0.0001$) or benzodiazepine (unipolar mania 55%, bipolar disorder 87%, $p=0.009$) treatment. There were no differences in lifetime history of treatment with atypical or typical antipsychotics; lithium, valproate or carbamazepine mood stabilisers; receiving combinations of mood stabilisers or receiving electroconvulsive therapy.

Discussion

In this study, we identified and characterised 30 people with unipolar mania in the United Kingdom and France. In the UK South London group, we identified 17 people with bipolar disorder who, over a ten-year follow-up period, have only experienced manic episodes and did not experience any documented depressive episodes. In the French group, we identified 13 people with bipolar disorder who from their semi-structured psychiatric assessment had only experienced manic or hypomanic episodes for at least 10 years and had never experienced a major depressive episode. Our study is the first to identify and characterise people with unipolar mania in the United Kingdom and only the second to do so in France.

The frequency of unipolar mania as a percentage of the bipolar disorder population was broadly similar in the two cohorts; 1.2% (17/1458) for the South London cohort and 3.3% (13/392) for the French cohort. We would speculate that, given the potential difficulties in identifying patients with unipolar mania in electronic clinical case records, the true frequency of unipolar mania as a percentage of the bipolar population in South London is likely to be higher. The rates of unipolar mania in the bipolar disorder population identified from our study is similar to the 5% rate reported in the USA (Baek et al., 2014), using similar unipolar mania criteria to ours, and to the 8.7% rate reported in Switzerland (Angst et al., 2004). It is however markedly lower than the 21% rate reported by Perugi et al. in an Italian inpatient bipolar sample (Perugi et al., 2007). This difference may be due to differences in exclusion criteria, for example the Perugi et al. study included people who had experienced a mixed episode as unipolar mania cases whereas ours excluded them. This underlines the need to develop a widely accepted clinical criteria for unipolar mania. Our study reinforces that people with unipolar mania can be identified in European countries and our findings suggest that people with unipolar mania may make up around 3% of the population of people with bipolar disorder in the UK and France.

Our results add to the evidence that the prevalence of unipolar mania amongst people with bipolar disorder is significantly lower in developed countries compared to developing countries. For example, our results contrast markedly to studies from Tunisia, Fiji, India and Nigeria which, using similar unipolar mania criteria to ours, report that at least 40% of people with bipolar disorder fulfilled criteria for unipolar mania (Aghanwa, 2001; Dakhlaoui et al., 2008; Khanna et al., 1992; Makanjuola, 1985). We also found interesting differences in the ethnicity of people with unipolar mania in South London compared to the bipolar disorder population, with a higher frequency than expected of people with unipolar mania of African ethnicity and lower frequency of white British ethnicity, albeit within a small sample size. This finding is similar to those reported by Baek et al in the United States who found that unipolar mania was more common in non-white people (Baek et al., 2014). We would suggest that future studies investigate differences in the prevalence of unipolar mania between developed and developing countries, and the potential role of ethnicity factors in mediating unipolar mania.

This study identified differences in the clinical characteristics of people with unipolar mania compared to people with bipolar disorder who have experienced depressive episodes. A clear finding from both cohorts was that people with unipolar mania experienced more manic episodes, 1.7 times more episodes in the UK cohort and 2.5 times more episodes in the French cohort, even though there were no differences between groups in the total overall number of mood episodes experienced (mania, hypomania, mixed and depressive). Our finding of an increased frequency of manic episodes experienced by people with unipolar mania has been previously reported by several other studies (Baek et al., 2014; Perugi et al., 2007). In contradiction to our hypothesis, we found no difference in the age of onset of bipolar disorder experienced by people with unipolar mania compared to people with bipolar disorder who have experienced depression in either cohort. People with unipolar mania in the French cohort were around three times more likely to experience psychotic symptoms during their first manic episode than people with bipolar disorder who have experienced depression. This finding concords with previous studies which report that people with unipolar mania are more likely to experience a psychotic illness onset (Andrade-Nascimento et al., 2011; Yazici et al., 2002). We were not able to examine this in the UK cohort as all first manic episodes in this cohort occurred before the inception date of the electronic clinical record system in 2005/6 which meant that there was often a limited clinical description available from uploaded previous records. There was however no increase in either cohort of the numbers of people with unipolar mania who had a lifetime history of psychosis compared to people with bipolar disorder who have experienced depressive episodes. People with unipolar mania in the French cohort also experienced more psychiatric hospital admissions but this finding was not replicated in the UK cohort potentially because of differences in mental health service provision between the two countries.

We found no differences in the self-harm risk profiles, or rates of substance use disorder and anxiety disorder co-morbidities in people with unipolar mania compared to people with bipolar disorder who had experienced depressive episodes. Importantly, the lack of association between substance use and unipolar mania implies that unipolar mania is not mediated by increased rates of the use of stimulants or other drugs which may induce mania. There was also no evidence in either cohort that people with unipolar mania were significantly less likely have a history of suicide attempts. This finding is similar to that reported by Perugi et al (Perugi et al., 2007) and may not support the concept that people with unipolar mania are at less risk of self-harm and suicide as they do not experience depressive episodes. These findings should to be considered in the context of the small unipolar mania sample size which may have been underpowered to detect relatively rare events such as suicide attempts.

Although we found clear differences in the clinical characteristics between the unipolar mania and bipolar disorder groups, their treatment characteristics were broadly similar. We found no differences between the two groups in antipsychotic treatment history, lithium or other mood stabiliser treatment history, or a history of combinations of mood stabilisers and antipsychotics. The main exception was that people with unipolar mania were significantly less likely to be treated with antidepressants, which would be expected as they have not experienced depressive episodes, and the French cohort were significantly less likely to be treated with benzodiazepines. As we found no major differences in the principal pharmacological treatment approaches for bipolar disorder between the two groups this may imply that unipolar mania is not a consequence of lack of appropriate treatment.

Limitations and strengths

A key strength of this study is that we identified people with unipolar mania who had experienced a very long duration of illness; in the UK cohort the mean duration was approximately 20 years and in the French cohort it was 23 years. This addresses the concern that depressive episodes may be missed in this population due to insufficient longitudinal observation. We also applied a very strict unipolar mania criteria including only people who had experienced at least three manic episodes and excluding people who had experienced any depressive or mixed episodes. Our study also identified and characterised people with unipolar mania in two geographically distinct but developmentally advanced Western European populations.

There are several limitations to this study. We were only able to identify a relatively small number of people with unipolar mania in each cohort which limits the power of the study to detect differences in clinical variables. Despite this, in both cohorts we identified differences in the frequency of manic episodes experienced. We were also unable to investigate ethnicity in the French cohort as this group originated from a study designed to investigate the genetic and environmental risk factors of bipolar disorder in which all participants were Caucasian French. A small number of people

with unipolar mania individuals had a history of being treated with antidepressants. These medications may have been used to treat co-morbid anxiety symptoms rather than depressive symptoms and there were no documented major depressive episodes in either unipolar mania cohorts. Finally, given the retrospective nature of the French cohort, and that SLAM electronic clinical records system began in 2005/6 with some previous records also uploaded, depressive episodes may have been missed due to reporting bias. However depressive episodes were assessed using a validated semi-structured interview in the French cohort, and uploaded records prior to 2005/6 or clinical references to symptoms prior to this date were searched and recorded in the South London study.

Conclusions

This study adds to the literature that people with unipolar mania can be identified in western developed countries at a prevalence rate of between 1-3% of the overall bipolar disorder population. This suggests that there are at least 19,000 people with unipolar mania living in the UK or France based on a 1% prevalence rate of bipolar I disorder (Merikangas et al., 2007). Our study provides further evidence that people with unipolar mania may experience an increased frequency of manic episodes but does not support the notion that they experience an earlier age of onset, are more likely to experience a history of psychosis or are at lower risk of self-harm. We have shown that it is possible to identify an uncoupling of mania from depression, as has been suggested by Hickie and others (Hickie, 2014), in two European bipolar disorder populations. Our findings call for larger prospective studies of unipolar mania in developed countries to better define prevalence, clinical characteristics and treatment response.

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